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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,884	07/22/2003	Richard Harkins	51791AUSC1	1667

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	

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06/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/624,884	HARKINS ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,31 and 33-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-31 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 May 2007 has been entered.

2. For the record, it is noted that while Applicants cannot, as a matter of right, obtain continued examination on claims that are independent and distinct from the invention previously claimed (i.e., applicants cannot switch inventions when filing an RCE) (MPEP 706.07(h)), applicant has reached an agreement with the examiner, in which applicant will switch the invention in the present RCE filing to an independent and distinct invention as set forth in the restriction requirement mailed 5/3/2006. In the response filed 5/14/2007, applicant elects the invention of Group IV. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-29 and 32 are cancelled.
Claims 30 and 33-35 have been amended.
Claims 36-37 have been added.

4. Claims 30-31 and 33-37 are pending and under consideration.

5. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

6. *All of the objections and rejections in the previous Office Action mailed 12/11/2006 are withdrawn unless otherwise indicated below, in view of the amendments to the specification and the cancellation of claims 1-25.*

Response to Arguments

7. The objection to the specification at pg. 39 as containing the hyperlink www.genweb.com is maintained.

The response filed 5/14/2007 does not change the hyperlink www.genweb.com as originally presented and the rejection is maintained. Spelling out the term "www" as "World Wide Web" would inactivate the hyperlink and overcome this objection. See MPEP § 608.01.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 5/14/2007 has introduced matter into the claims. Newly added claim 36 recites wherein the detectable marker of the immunoconjugate of the claimed immodetection method is a radioisotope, a fluorescent compound, a bioluminescent compound, chemiluminescent compound, a metal chelator or an enzyme. The response filed 5/14/2007 points to pg. 31, lines 19-22 and pg. 37 lines 10-12 of the as-filed specification for support, however, the specification as pointed to discloses the presently claimed detectable markers in the context of diagnostic tests and assays using samples obtained from a patient, including radioimmunoassays, competitive-binding assays, western Blot analysis and enzyme-linked immunoabsorbant assays, fluorescent activated cell sorting, and surface plasmon resonance, which are all

assays performed *ex vivo*, whereas the claims are presently drawn to detecting a disease-state in a subject, i.e., *in vivo* detection, not in a sample obtained from a patient. The presently claimed detectable markers of claim 36 are not disclosed in the as-filed specification in the context of a detection method that is performed in a subject, i.e., *in vivo*. Newly presented claim 36 now recites limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in newly added claim 36, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in newly added claim 36 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

10. Claims 30-31 and 33-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a disease-state in a subject associated with the expression of RG1 (SEQ ID NO:2) comprising administering an immunoconjugate comprising an antibody or antigen-binding fragment thereof that specifically binds RG1 (SEQ ID NO:2), wherein an increased level of binding in the compared to disease free control subjects is indicative of a disease state, does not reasonably provide enablement for said method of detecting a disease state in a subject comprising administering an immunoconjugate comprising an antibody variant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).
Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered antibodies and immunodiagnosis where the relative level of skill of those in the art is deemed to be high.

The claims are broadly drawn to the immunodiagnosis of diseases expressing RG1 comprising administering an immunoconjugate comprising an antibody or fragment thereof or variant thereof that specifically binds RG1 (SEQ ID NO:2), wherein the antibody variants are disclosed in the specification as comprising a light chain variable region having at least 80% amino acid sequence identity with SEQ ID NO:26 or 29, or comprising a heavy chain variable region having at least 80% amino acid sequence identity with SEQ ID NO:27, 28, 30 or 31, wherein the variants may include amino acid substitutions, deletions and insertions (e.g., see pp. 32-35). Thus, the claims broadly encompass antibodies comprising a modified variable region or regions comprising amino acid insertions, deletions and/or substitutions, inclusive to antibodies that do not contain a full set of 6 CDRs, three from the heavy chain variable region and three from the light chain variable region and do not bind RG1.

The specification discloses only antibodies that specifically bind RG1 and comprise all 6 CDRs, three from the heavy chain variable region and three from the light chain variable region (e.g., see Examples 4-12). The specification does not teach antibody variants that specifically bind RG1 or antibodies that do not contain all six CDRs, three from the heavy chain variable region and three from the light chain variable region that bind RG1 or antibodies comprising a light chain variable region having at least 80% amino acid sequence identity with SEQ ID NO:26 or 29, or comprising a heavy chain variable region having at least 80% amino acid sequence identity with SEQ ID NO:27, 28, 30 or 31, wherein the human antibodies bind RG1. There are no working examples of antibody variants that bind RG1. Thus, the scope of the claims is extremely broad relative to the teachings in the specification. The scope of the claims

must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions", cited on PTO-892 mailed 6/5/2006). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, March 1982, cited on PTO-892 mailed 6/5/2006). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Coleman (Research in Immunology, 145:33-36, 1994, cited on PTO-892 mailed 6/5/2006) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). It is unlikely that antibodies comprising a variable region having at least 80% sequence identity to the corresponding variable regions of the disclosed RG1 specific antibodies, or antibodies which do not contain all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite RG1 binding function. For

example, Hanson et al (U.S. Patent 6,682,736, cited on PTO-892 mailed 6/5/2006) teach a human monoclonal antibody comprising a light chain variable region that is 93% identical to the instantly claimed light chain variable region of SEQ ID NO:26 and the human antibody binds CTLA-4 (see Exhibit C attached to the Office Action mailed 6/5/2006). The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibodies comprising a light chain variable region having at least 80% sequence identity with SEQ ID NO:26 or 29 or comprising a heavy chain variable region having at least 80% sequence identity with SEQ ID NO:27, 28, 30 or 31, and/or less than all six CDRs that bind RG1 (SEQ ID NO:2) from a parent RG1 specific antibody. Although the specification at pg. 35 discloses that antibody variants can be made using any techniques and provides guidelines for conservative and non-conservative mutations, and the antibody variants may include amino acid substitutions, deletions or insertions, particularly, substituting one or more hypervariable regions (i.e., CDR) residues, the specification does not provide sufficient guidance or direction as to the general tolerance to modification and extent of such tolerance in the variable regions or CDRs; the specific positions of the variable regions or CDRs which can be predictably modified and which regions are critical for maintaining specificity and affinity for RG1. The specification provides no direction or guidance regarding how to produce the myriad of variant antibodies, which contain a modified variable region as broadly defined by the claims. "(A) specification which describes' does not necessarily also enable' one skilled in the art to make or use the claimed invention." See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975). Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, Coleman P. M. and Hanson et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed antibody variants that bind RG1 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibody

variants and absent working examples providing evidence which is reasonably predictive that the claimed antibody variants bind RG1, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 30-31 and 33-37 are rejected under 35 U.S.C. 102(e) as being unpatentable over Ali et al (US 2005/0147556 A1, priority to 10/19/1998, cited on PTO-892 mailed 6/5/2006).

Ali et al teach a method of detecting, diagnosing or staging of prostate cancer in a patient comprising administering an antibody (i.e., polyclonal, monoclonal, ect) that specifically binds to a prostate cancer polypeptide (i.e., SEQ ID NO:2; "CSG") that is 99% identical to the claimed RG1 polypeptide of SEQ ID NO:2 (see Exhibit B attached to the Office Action mailed 6/5/2006), wherein the antibody is conjugated to a radioisotope (^{67}Cu, ^{186}Re, ^{111}In or ^{99m}Tc), paramagnetic metal, positron emitting labels, and detecting the immunoconjugate by radioimmunoscintographic imaging, magnetic resonance imaging and positron emitting tomography, wherein an increase in CSG levels in the human patient versus a normal human control is associated with prostate cancer (see entire document, particularly pages 2-3 and 4 and SEQ ID NO:2). Given the substantial structural identity of the polypeptide of the prior art and the claimed polypeptide of SEQ ID NO:2 (i.e., 99% sequence identity), one of ordinary skill in the art would reasonably conclude that Ali et al's antibodies also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Ali et al have produced antibodies that are identical to the claimed

antibodies. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibodies with the antibodies of Ali et al, the burden of proof is upon Applicant to show a distinction between the structural and functional characteristics of the claimed antibodies and the antibodies of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See MPEP 2112.01.

Thus, Ali et al anticipate the claims.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 30-31 and 33-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-36 of copending Application No. 10/895,183.

The claims in the present application are drawn to a method of detecting a disease-state in a subject, wherein the disease-state is associated with expression of an RG1 polypeptide having the amino acid sequence of SEQ ID NO:2, and wherein the method comprises: (a) administering to the subject an immunoconjugate wherein the immunoconjugate comprises an antibody or a fragment or a variant thereof that specifically binds to an epitope present in the RG1 polypeptide having the amino acid sequence of SEQ ID NO: 2 and wherein the antibody or the fragment or the variant thereof is conjugated to a molecule which is a detectable marker; (b) detecting the immunoconjugate and (c) determining if the level of binding of the immunoconjugate is increased as compared with the level of binding detected in disease-free control subjects, an increased level being indicative of a disease state, wherein detection is by immunoscintigraphy or positron emitting tomography and the disease state is prostate cancer and the antibody is a polyclonal, monoclonal, chimeric, humanized or full-human antibody.

Claims 30-36 of copending Application No. 10/895,183 are also drawn to a method of detecting a disease-state in a subject, wherein the disease-state is associated with expression of an RG1 polypeptide having the amino acid sequence of SEQ ID NO: 2, and wherein the method comprises: (a) administering to the subject the immunoconjugate comprising an antibody conjugated to a radiolabel, an enzyme, a chromophore, or a fluorescer; (b) detecting the binding of the immunoconjugate within the subject; and (c) determining if the level of binding of the immunoconjugate in the subject is increased as compared with the level of binding detected in disease-free control subjects, wherein detection is by immunoscintigraphy or positron emitting tomography and the disease state is prostate cancer and the antibody is a monoclonal antibody.

Thus, claims 30-36 of copending Application No. 10/895,183 are drawn to an invention that reads upon the invention claimed in the present application and hence, is not patentably distinct from the invention claimed in the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 30-31 and 34-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-11 of U.S. Patent No. 6,682,902 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 10-11 of U.S. Patent No. 6,682,902 B2 are drawn to a method of detecting metastasis of prostate cancer in a subject, wherein the method comprises: (a) injecting the subject with an appropriate dose of a radiolabeled antibody or antibody-fragment which specifically binds to one or more epitopes present in a human RG1 polypeptide having the amino acid sequence of SEQ ID NO: 2; (b) detecting by immunoscintography the binding of the radiolabeled antibody or antibody fragment to one or more epitopes present in the human RG1 polypeptide within the subject; and (c) determining if the level of binding in the subject is increased over the level detected in normal controls wherein the radiolabel is In-111 or tc-99m. Thus, claims 10-11 of U.S. Patent No. 6,682,902 B2 are drawn to an invention that reads upon the invention claimed in the present applications and hence, is not patentably distinct from the invention claimed in the present application.

Claims 30-31 and 34-37 are directed to an invention not patentably distinct from claims 10-11 of commonly assigned U.S. Patent 6,682,902 B2. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent 6,682,902 B2 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

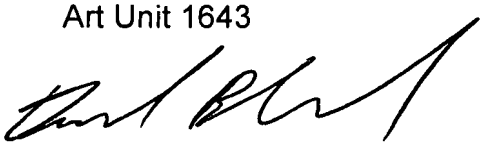
16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard
Primary Examiner
Art Unit 1643



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May 25, 2007